IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

SCHWEIGHOFFER et al. Atty. Ref.: 3665-167; Confirmation No. 5165

Appl. No. 10/560,774 TC/A.U. 1617

Filed: December 14, 2005 Examiner: Javanmard

For: USE OF PYRAZOLOPYRIDINES FOR THE TREATMENT OF COGNITIVE DEFICITS

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

I, Peter J. Snyder, Ph.D., do hereby declare and say as follows:

1. I am Vice President for Research, Institutional Official & Scientific Integrity Officer, Lifespan Affiliated Hospitals, Providence, RI; Professor, Department of Neurology, The Warren Alpert Medical School of Brown University; Adjunct Professor, Child Study Center, Yale University School of Medicine, New Haven, CT; and Associate Editor, *Brain & Cognition*. I am a clinical neuropsychologist who has examined, diagnosed and treated patients with Alzheimer's Disease since 1992. I received my Ph.D. from Michigan State University (East Lansing, MI) in 1992, and I completed my clinical internship and post-doctoral fellowship at the Albert Einstein College of Medicine (Long Island Jewish Medical Center) from 1992 through 1994.

2. I have reviewed the above-identified application as well as the claims. I understand the following to be the claims of the above:

> Claim 13. A method of improving perceptive cognition in a patient in need thereof, the method comprising administering to the patient an effective amount of etazolate, and monitoring said patient for improvement in perceptive cognition after said administering.
>
> Claim 12. The method of claim 13, wherein the composition is administered orally or systemically.
>
> Claim 14. The method of claim 13, wherein the patient has Alzheimer's disease.

3. I have reviewed Ikhlef (U.S. Patent Application Publication No. 2003/0064374) and Schumcher (U.S. Patent No. 7,153,871), as I have been advised by the European agent of the Assignee, EXONHIT THERAPEUTICS SA (ExonHit), that the U.S. Patent Office official in charge of the above (the Examiner) has asserted that it would have been obvious to have made the claimed invention from the combination of these references.

4. I believe that one of ordinary skill in the art would not have appreciated, from the combination of Ikhlef and Schumcher, the unexpected benefit of administering etazolate to improve perceptive cognition in a patient in need thereof, as claimed.

5. Alzheimer's disease (AD) is a multimodal pathology for which the cause and progression are still not well understood. Research indicates that the disease is associated with cerebral plaques laden with β-amyloid peptide (Aβ) as well as prominent neurofibrillary tangles (with a preponderance of these found in medial temporal-lobe structures). Other neuropathological correlates of AD include a loss of neurons and white matter, congophilic (amyloid) angiopathy, inflammation, and diffuse

oxidative damage. Symptoms of Alzheimer's disease vary across individuals and typically include inability to acquire new memories (such as difficulty in recalling recently observed facts), confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline. Gradually, bodily functions are lost, ultimately leading to death.

6. Because patients suffering from Alzheimer's disease are prescribed drugs designed to halt or slow the progression of the deleterious cognitive changes described above, it is sometimes, mistakenly, thought that Alzheimer's disease only involves cognitive deficits. It is also sometimes, mistakenly, thought that treating Alzheimer's disease equals treating the cognitive symptoms and, conversely, that by improving cognitive symptoms the disease course itself is being modified. This assumption, however, misses fundamental points: While cognitive decline is typically associated with Alzheimer's disease, it is a consequence of the disease and is not limited to or exclusively associated with Alzheimer's disease. Furthermore, many drugs designed to treat Alzheimer's disease have no effect on cognition. As an illustration of this point, Holmes C et al. (Lancet 2008;372:216-223) (attached) have shown that an anti-amyloid vaccine that appeared to clear amyloid plaques in the brain had no effect on cognition. As stated page 221, right column,

> "despite the evidence of disease modification, there is little evidence to suggest that there is any major effect on cognitive function".

In other words, no effect on cognition was observed in immunized subjects.

7. Etazolate is now recognized as a disease modifier. None of the drugs currently approved for Alzheimer's disease act on the underlying mechanisms of the

disease or modify the progression of the disease. The symptomatic benefits they confer are therefore only temporary and often disappear once the patient stops taking these drugs or as the severity of the underlying neuropathology increases over time.

8. ExonHit has surprisingly demonstrated both *in vitro* and *in vivo* that etazolate enhances the activity of alpha-secretase, thereby interfering with the usual processing of the amyloid precussor protein (APP) to increase the production of soluble APPalpha (sAPP-alpha) and reduce the production of amyloid-beta (Abeta), the main component of the plaques which accumulate in the brains of Alzheimer's disease patients. In addition, sAPP-alpha protects cortical cells against the toxicity induced by Abeta. It is believed that stopping or slowing the progression of Abeta plaque formation could have a fundamental impact on the evolution of Alzheimer's disease and etazolate is considered as a potential "disease modifier" for this pathology.

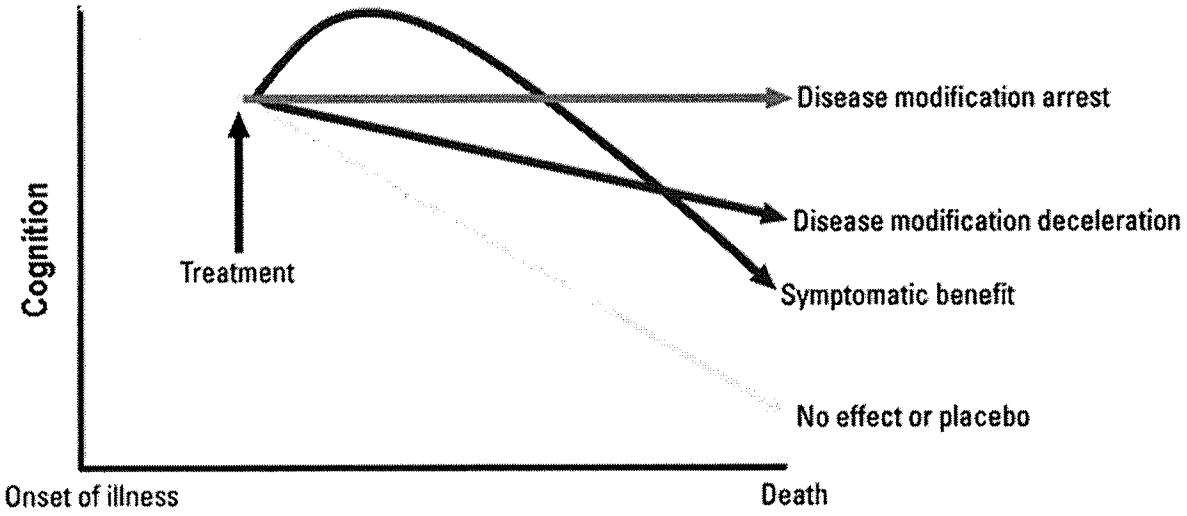
9. Etazolate has also been surprisingly found to further act on cognition. I am a co-author on a manuscript that is currently under review in a peer-reviewed journal, in which we present the results of a phase IIA clinical trial that demonstrate a beneficial effect of this drug in slowing progression of cognitive change as measured by the ADAS-Cog scale. This effect was strengthened by the lower number of rapid decliners (having worsened by at least 4 points in ADAS-Cog throughout the study) observed in the etazolate groups compared to the placebo group. Moreover, in that same study we showed that in patients who are positive for the ApoE4 allele (having one or 2 ApoE4 alleles) – that is, the subgroup of subjects who are most at risk for the disease as a result of having this known genetic risk factor – there was an indication of treatment-related improvement on several cognitive scales included as secondary endpoints in

the trial. Hence, in addition to the capacity of etazolate to act on Abeta plaque formation, it also appears to protect and/or improve cognitive functioning.

10. There is no indication in Ikhlef and/or Schumcher, and no precedent in the art that I am aware of, that stopping plaque progression would have been expected to lead to enhanced cognition. At the time of filing the present application (i.e., 2003-2004) as well as presently, it would not have been expected by one of ordinary skill in the art that a disease modifying drug would lead to an "improvement in perceptive cognition after [...] administering", even in healthy subjects, as described in the present application. To the contrary, there have recently been reports of several failed clinical trials in which amyloid plaque burden was reduced with treatment, but without any concomitant changes in cognition or behavioural symptoms.

11. In contrast, as illustrated in the figure below, such drugs may at best have been expected to only lead to a reduction in the decline of such cognition, or to a stabilization of cognition, leaving the patients to take other drugs in order to improve their cognition.

DISEASE MODIFICATION VERSUS SYMPTOMATIC BENEFIT IN THE TREATMENT OF ALZHEIMER'S DISEASE



Adapted from Kennedy GJ. *Primary Psychiatry*. Vol14, No 11. 2007.

12. Etazolate surprisingly, and most remarkably, has a pro-cognitive effect. As discussed below, this effect is pronounced and it is deemed to be independent from the disease modifying effect: This surprising effect is linked to etazolate's effect on $GABA_A$ as well as to sAPP-alpha's procognitive effect; it has been observed after single administration of etazolate whereas the disease modifying effect is unlikely to have any observable impact over short-term administration; and this effect has been observed in normal rats, not suffering from AD-like symptoms.

13. The neuroprotective effects and disease modifying properties of etazolate are likely to be disconnected from procognitive effects. The neuroprotective effects and the procognitive ones cannot be inferred from one another because they are linked to, respectively, a positive and a negative modulation of the $GABA_A$ receptor

pharmacology, the positive one being associated with amnestic effects while the negative is linked to procognition.

14. Etazolate surprisingly shows both symptomatic and disease modifying properties, which are independently derived from its multi-modal mechanism of action. Etazolate's effect on cognition could not have been predicted from prior art.

15. In 2003, at the time the present invention was made, only very few studies investigated or reported a potential effect of PDE4 inhibition on memory. Indeed, prior to 2003, while about 400 publications were released on PDE4, only 7 thereof (i.e., less than 2%) appear to refer to memory or cognition (see for example, Miró X, et al. "Differential distribution of cAMP-specific phosphodiesterase 7A mRNA in rat brain and peripheral organs." Synapse. 2001 Jun 1;40(3):201-14 (Abstract); Thompson BE, et al. "Cyclic AMP phosphodiesterases in the zebra finch: distribution, cloning and characterization of a PDE4B homolog." Brain Res Mol Brain Res. 2000 Nov 10;83(1-2):94-106 (Abstract); Zhang HT, et al. "Inhibition of cyclic AMP phosphodiesterase (PDE4) reverses memory deficits associated with NMDA receptor antagonism." Neuropsychopharmacology. 2000 Aug;23(2):198-204 (Abstract); Zhang HT, et al. "Effects of rolipram on scopolamine-induced impairment of working and reference memory in the radial-arm maze tests in rats." Psychopharmacology (Berl). 2000 Jun;150(3):311-6 (Abstract); Cherry JA, et al. "Cyclic AMP phosphodiesterases are localized in regions of the mouse brain associated with reinforcement, movement, and affect." J Comp Neurol. 1999 May 3;407(2):287-301 (Abstract); Barad M, et al., "Rolipram, a type IV-specific phosphodiesterase inhibitor, facilitates the establishment of long-lasting long-term potentiation and improves memory." Proc Natl Acad Sci U S

A. 1998 Dec 8;95(25):15020-5 (Abstract); and Egawa T, et al., "Rolipram and its optical isomers, phosphodiesterase 4 inhibitors, attenuated the scopolamine-induced impairments of learning and memory in rats." Jpn J Pharmacol 1997 Nov;75(3):275-81 (Abstract), (attached)).

16. Furthermore, when referring to cognition, these publications essentially always relate to the same PDE4 inhibitor, rolipram. In particular, these references, published between 1997 and 2001, refer to work conducted with rolipram only. However, these publications are essentially conditional and contain no or contradictory results. Indeed, in 2003, Ramos et al ("Dysregulation of Protein Kinase A Signaling in the Aged Prefrontal Cortex: New Strategy for Treating Age-Related Cognitive Decline" Neuron, Vol. 40, 835–845, November 13, 2003) investigated the effect of Rolipram on rats and monkeys. The results published show that, while Rolipram improved cognition in rats, the same compound substantially impaired memory or cognition in aged monkeys. As stated page 838, right column, first paragraph:

> "in contrast to rolipram's beneficial influence on hippocampal-dependent memory functions in aged mice, rolipram impaired working memory performance in aged monkeys".

17. These results thus show that, in 2003, the effect of PDE4 inhibition in cognition was not established and would not have been reasonably expected by one of ordinary skill in the art.

18. At the time the application was filed, in 2003, PDE4 inhibitors were mostly used for inflammatory diseases. Today, most reports also relate to inflammation. See for instance the review by D. Spina ("PDE4 inhibitors: current status" 2008 British

Journal of Pharmacology 155, 308-315) (attached), dated 2008, which does not mention cognition. Also, as of today, among 172 PDE4 inhibitors which have been disclosed in preclinical or clinical settings, only 13 (i.e., less than 8%) have been considered as potential cognition enhancers. Furthermore, out of these 13 inhibitors, 9 have been discontinued or lack any development report. These data demonstrate that, in the wide area of PDE inhibition, the ordinarily skilled person may have been inclined to associate PDE4 inhibitors to inflammatory diseases, but would not have reasonably expected that a PDE4 inhibitor could be used to improve cognition.

19. At the time the present invention was made, there was no disclosure of any effect of Etazolate on cognition. At the time the present invention was made, there was no established correlation between PDE4 inhibition and cognition, and there was essentially contradictory data.

20. The discovery, by the applicants, that Etazolate improves cognition, even in normal animals, was in my opinion unexpected and surprising.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 23rd day of September, 2010.

(Signature) _____

Peter J. Snyder, Ph.D.